L4 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2000 ACS

TI Novel macrocyclic inhibitors of matrix metalloproteinases and **TNF -.alpha. converting** enzyme.

AU Decicco, Carl P.; Nelson, David J.; Kennedy, Ken; Hardman, Karl; Copeland, Robert; Covington, Maryanne; Magolda, Ron; Arner, Elizabeth; Duan, Jim; et al.

SO Book of Abstracts, 214th ACS National Meeting, Las Vegas, NV, September 7-11 (1997), MEDI-100 Publisher: American Chemical Society, Washington, D. C.
CODEN: 64RNAO

AB A novel series of macrocyclic inhibitors of MMPs and **TACE** have been prepd. and studied as potential therapeutic agents for arthritis. New methodol. for the prepn. of the anti-succinate moiety and P2' linker region has also been developed. The design and prepn. of these mols., the **x-ray crystal** structure of inhibitor bound complexes to MMP-3, and the in vitro profile for these compds. will be presented.

Nature 385(6618) pp. 733-36

(FILE 'HOME' ENTERED AT 16:06:13 ON 18 JUL 2000)

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE, LIFESCI, SCISEARCH, TOXLINE, CABA,
BIOTECHNO' ENTERED AT 16:06:16 ON 18 JUL 2000
L1 177906 S TNF(W)ALPHA OR TNF?
L2 234 S ((TNF(W)ALPHA) (3W) (CONVERTING OR CONVERTASE)) AND TACE
L3 11 S L2 AND (CRYSTAL OR X(W)RAY)
L4 5 DUP REM L3 (6 DUPLICATES REMOVED)
L5 370 S ((TNF(W)ALPHA) (3W) (CONVERTING OR CONVERTASE))
L6 13 S L5 AND (METALLOPROTEINASE? OR ENDOPEPTIDASE) AND (CRYSTAL OR
L7 7 DUP REM L6 (6 DUPLICATES REMOVED)
L8 29 S L1 AND (METALLOPROTEINASE? OR ENDOPEPTIDASE) AND (CRYSTAL OR
L9 15 DUP REM L8 (14 DUPLICATES REMOVED)

L9 ANSWER 6 OF 15 BIOSIS COPYRIGHT 2000 BIOSIS
TI ***Crystal*** structure of the catalytic domain of human ***TNFalpha*** -converting enzyme.
AU Maskos, Klaus (1); Fernandez-Catalan, Carlos (1); Huber, Robert (1); Bourenkov, Gleb P.; Bartunik, Hans; Ellestad, George A.; Reddy, Pranitha;
Wolfson, Martin F.; Rauch, Charles T.; Castner, Beverly J.; Davis, Raymond; Clarke, Howard R. G.; Petersen, Melissa; Fitzner, Jeffrey N.; Cerretti, Douglas Pat; March, Carl J.; Paxton, Raymond J.; Black, Roy A.;
Bode, Wolfram (1)
SO Journal of Interferon and Cytokine Research, (May, 1998) Vol. 18, No. 5, pp. A14.
Meeting Info.: 7th International Conference on Tumor Necrosis Factor and Related Molecules Scientific Advances and Medical Applications Hyannis, Massachusetts, USA May 17-21, 1998
ISSN: 1079-9907.
TI ***Crystal*** structure of the catalytic domain of human ***TNFalpha*** -converting enzyme.
IT . . .
and Molecular Biophysics)
IT Chemicals & Biochemicals
membrane-anchored proteinase; tumor necrosis factor-alpha; tumor necrosis factor-alpha converting enzyme [TACE]: catalytic domain ***crystal*** structure, human, ***metalloproteinase***
RN 81669-70-7 (***METALLOPROTEINASE***)
9001-92-7 (PROTEINASE)

L9 ANSWER 11 OF 15 BIOSIS COPYRIGHT 2000 BIOSIS
TI Novel cyclophane inhibitors of matrix ***metalloproteinases*** and ***TNF*** - ***alpha*** converting enzyme.
AU Decicco, Carl P.; Nelson, David J.; Xue, C.-B.; Hardman, Karl; Copeland, Robert; Covington, Maryanne; Magolda, Ron; Arner, Elizabeth
SO Abstracts of Papers American Chemical Society, (1997) Vol. 214, No. 1-2, pp. MEDI 96.
Meeting Info.: 214th American Chemical Society National Meeting Las Vegas,
Nevada, USA September 7-11, 1997
ISSN: 0065-7727.
TI Novel cyclophane inhibitors of matrix ***metalloproteinases*** and ***TNF*** - ***alpha*** converting enzyme.
IT Major Concepts
Biochemistry and Molecular Biophysics; Enzymology (Biochemistry and Molecular Biophysics); Methods and Techniques; Pharmacology
IT Chemicals & Biochemicals
METALLOPROTEINASES
IT Miscellaneous Descriptors
CHEMICAL SYNTHESIS; ***CRYSTAL*** STRUCTURE; CYCLOPHANE COMPOUNDS;
ENZYME INHIBITOR-DRUG; MATRIX ***METALLOPROTEINASE*** INHIBITORS; MATRIX ***METALLOPROTEINASES*** ; PHARMACOLOGY; SC903; TUMOR NECROSIS FACTOR-ALPHA CONVERTING ENZYME; TUMOR NECROSIS FACTOR-ALPHA CONVERTING ENZYME INHIBITORS
RN 81669-70-7D (***METALLOPROTEINASES***)

=> d ti au so kwic 10

L9 ANSWER 10 OF 15 BIOSIS COPYRIGHT 2000 BIOSIS
TI Novel macrocyclic inhibitors of matrix ***metalloproteinase*** and ***TNF*** - ***alpha*** converting enzyme.
AU Decicco, Carl P.; Nelson, David J.; Kennedy, Ken; Hardman, Karl; Copeland,
Robert; Covington, Maryanne; Magolda, Ron; Arner, Elizabeth; Duan, Jim; Cherney, Robert; Xue, C.-B.
SO Abstracts of Papers American Chemical Society, (1997) Vol. 214, No. 1-2, pp. MEDI 100.
Meeting Info.: 214th American Chemical Society National Meeting Las Vegas,
Nevada, USA September 7-11, 1997
ISSN: 0065-7727.
TI Novel macrocyclic inhibitors of matrix ***metalloproteinase*** and ***TNF*** - ***alpha*** converting enzyme.
IT Major Concepts
Biochemistry and Molecular Biophysics; Enzymology (Biochemistry and Molecular Biophysics); Methods and Techniques; Pharmacology
IT Chemicals & Biochemicals
METALLOPROTEINASE
IT Miscellaneous Descriptors
CHEMICAL SYNTHESIS; ENZYME-INHIBITOR COMPLEX; MACROCYCLIC COMPOUNDS; MATRIX ***METALLOPROTEINASE*** -3; ***METALLOPROTEINASE*** INHIBITORS; MMP-3; PHARMACOLOGY; TUMOR NECROSIS FACTOR-ALPHA CONVERTING
ENZYME; ***X*** - ***RAY*** ***CRYSTAL*** STRUCTURE
RN 81669-70-7 (***METALLOPROTEINASE***)

=> d ti au so kwic 9

L9 ANSWER 9 OF 15 CAPLUS COPYRIGHT 2000 ACS
TI Rational design of matrix ***metalloproteinase*** inhibitors: A novel
series of macrocyclic compounds featuring a linkage between the P1 and P2'
residues.
AU Xue, C. -B.; He, X.; Roderick, J.; Hardman, K.; Copeland, R.; Jaffee, B.;
Arner, E.; Magolda, R.; DeGrado, W. F.; Decicco, C.
SO Book of Abstracts, 214th ACS National Meeting, Las Vegas, NV, September 7-11 (1997), MEDI-095 Publisher: American Chemical Society, Washington, D.
C.
CODEN: 64RNAO
TI Rational design of matrix ***metalloproteinase*** inhibitors: A novel
series of macrocyclic compounds featuring a linkage between the P1 and P2'
residues.
AB Succinate-based hydroxamic acid is a class of matrix ***metalloproteinase*** (MMP) inhibitors. Based on the structural characteristics of these inhibitors, we have designed a novel series of macrocyclic compds. using. . . (12-14 membered rings) and different linkers. These compds. are potent MMP inhibitors and showed good activity
in the inhibition of ***TNF*** -C. The ***crystal*** structure of
SC903 bound MMP-3 will also be presented.

=> d ti au so kwic 8

L9 ANSWER 8 OF 15 CAPLUS COPYRIGHT 2000 ACS
TI Novel macrocyclic inhibitors of matrix ***metalloproteinases*** and ***TNF*** -. ***alpha*** . converting enzyme.
AU Decicco, Carl P.; Nelson, David J.; Kennedy, Ken; Hardman, Karl; Copeland,
Robert; Covington, Maryanne; Magolda, Ron; Arner, Elizabeth; Duan, Jim; et
al.
SO Book of Abstracts, 214th ACS National Meeting, Las Vegas, NV, September 7-11 (1997), MEDI-100 Publisher: American Chemical Society, Washington, D.
C.
CODEN: 64RNAO
TI Novel macrocyclic inhibitors of matrix ***metalloproteinases*** and ***TNF*** -. ***alpha*** . converting enzyme.
AB . . . of the anti-succinate moiety and P2' linker region has also been
developed. The design and prepn. of these mols., the ***x*** - ***ray*** ***crystal*** structure of inhibitor bound complexes to
MMP-3, and the in vitro profile for these compds. will be presented.

=> d ti au so kwic 7

L9 ANSWER 7 OF 15 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.DUPLICATE 5
TI Cloning of a disintegrin ***metalloproteinase*** that processes precursor tumour-necrosis factor-.alpha..
AU Moss M.L.; Jin S.-L.C.; Milla M.E.; Burkhart W.; Carter H.L.; Chen W.-J.;
Clay W.C.; Didsbury J.R.; Hassler D.; Hoffman C.R.; Kost T.A.; Lambert M.H.; Leesnitzer M.A.; McCauley P.; Mageehan G.; Mitchell J.; Moyer M.; Pahel G.; Rocque W.; Overton L.K.; Schoenen F.; Seaton T.; Su J.-L.; Warner J.; Willard D.; Becherer J.D.
SO Nature, (1997) 385/6618 (733-736).
ISSN: 0028-0836 CODEN: NATUAS
TI Cloning of a disintegrin ***metalloproteinase*** that processes precursor tumour-necrosis factor-.alpha..
AB Tumour-necrosis factor-.alpha. (***TNF*** -. ***alpha*** .) is a cytokine that contributes to a variety of inflammatory disease states. The
protein exists as a membrane- bound precursor of relative molecular mass 26K which can be processed by a ***TNF*** -. ***alpha*** .-converting
enzyme (TACE), to generate secreted 17K mature ***TNF*** -. ***alpha*** .. We have purified TACE and cloned its complementary DNA.
TACE is a membrane- bound disintegrin ***metalloproteinase*** . Structural comparisons with other disintegrin-containing enzymes indicate
that TACE is unique, with noteable sequence identity to MADM, an enzyme implicated. . . for neuronal development. The expression of recombinant
TACE (rTACE) results in the production of functional enzyme that correctly
processes precursor ***TNF*** -. ***alpha*** . to the mature form. The rTACE provides a readily available source of enzyme to help in the search for new anti-inflammatory agents that target the final processing stage of ***TNF*** -. ***alpha*** . production.

L9 ANSWER 6 OF 15 BIOSIS COPYRIGHT 2000 BIOSIS
TI ***Crystal*** structure of the catalytic domain of human ***TNFalpha*** -converting enzyme.
AU Maskos, Klaus (1); Fernandez-Catalan, Carlos (1); Huber, Robert (1); Bourenkov, Gleb P.; Bartunik, Hans; Ellestad, George A.; Reddy, Pranitha;
Wolfson, Martin F.; Rauch, Charles T.; Castner, Beverly J.; Davis, Raymond; Clarke, Howard R. G.; Petersen, Melissa; Fitzner, Jeffrey N.; Cerretti, Douglas Pat; March, Carl J.; Paxton, Raymond J.; Black, Roy A.;
Bode, Wolfram (1)
SO Journal of Interferon and Cytokine Research, (May, 1998) Vol. 18, No. 5, pp. A14.

Meeting Info.: 7th International Conference on Tumor Necrosis Factor and Related Molecules Scientific Advances and Medical Applications Hyannis, Massachusetts, USA May 17-21, 1998
ISSN: 1079-9907.

TI ***Crystal*** structure of the catalytic domain of human ***TNFalpha*** -converting enzyme.
and Molecular Biophysics)

IT Chemicals & Biochemicals
membrane-anchored proteinase; tumor necrosis factor-alpha; tumor necrosis factor-alpha converting enzyme [TACE]: catalytic domain ***crystal*** structure, human, ***metalloproteinase***

RN 81669-70-7 (***METALLOPROTEINASE***)
9001-92-7 (PROTEINASE)

L17 ANSWER 3 OF 3 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
TI Analogs of 4-hydroxypyrone: Potent, non-peptidic HIV protease inhibitors.
AU Romines K.R.; Thaisrivongs S.
SO Drugs of the Future, (1995) 20/4 (377-382).
ISSN: 0377-8282 CODEN: DRFUD4
AB The research investigations described above are excellent examples of the potential of **structure**-based **drug design**.
Promising lead structures were identified from broad screening programs, and x-ray crystal structures of these leads bound to the HIV protease were obtained in a timely fashion. These x-ray crystallographic data were used to identify the 4-hydroxypyrone ring as the essential pharmacophore, and the data provided the basis for initial drug design work. Since derivatives of these new, non-peptidic lead structures were readily prepared, a number of analogs could be synthesized and evaluated in a relatively short period of time. One of the most important factors that contributed to the **success** of these programs, however, was the use of strategy based on an iterative cycle of inhibitor design. Continual **co-crystallization** of new inhibitors with the HIV protease and study of the structural information from the resulting x-ray crystallographic data played a critical role in achieving the dramatic increases in inhibitor potency described above. It is expected that this strategy will continue to produce even better inhibitors and that improved clinical candidates will be forthcoming from these structural classes. It is interesting to note some of the strengths and weaknesses of the various lead structures used in protease inhibitor research. In the case of peptide-derived structures, questions of potency were addressed first, and efforts to improve the pharmacokinetic parameters were undertaken at a later stage. The non-peptidic 4-hydroxycoumarin lead structures, however, already had proven pharmacokinetic profiles, warfarin and U29342 have even been used therapeutically as anticoagulant agents in man, but their enzyme inhibitory activity was weak. It is encouraging to note that as the more potent analogs, such as clinical candidate U96988, have been identified, the favorable pharmacokinetic profiles have not been lost. When the HIV protease was first identified as a possible target for therapeutic intervention, there was considerable optimism, due to the selective profile of HIV protease funcion, that a competitive inhibitor of this enzyme could avoid the development of drug resistance which has crippled the effectiveness of other agents, such as the nucleoside reverse transcriptase inhibitor AZT. However, recent improvements in our understanding of the dynamics of HIV infection, as well as new clinical data on HIV protease inhibitors, indicate that protease inhibitors are also very likely to encounter drug resistant strains of HIV. Research results from the laboratories of Shaw and Ho have demonstrated that HIV infection does not involve a period of dormancy, followed by rapid immune system decline, but rather is a constant raging battle between the virus and the host's, immune system which is gradually lost by the host over a period of months or years. These new studies of HIV protease inhibiors in HIV-infected patients shows that every day, billions of viral particles are produced by newly infected cells, and almost as rapidly, are cleared, resulting in what appears to be a steady state. The two peptide-derived protease inhibitors used in these studies, ABT-538 from Abbott and L-735,524 from Merck, showed a dramatic and rapid reduction in viral load. These results illustrate the rapid replication rate of the virus. The rapid replication rate of HIV is a key factor in its ability to quickly develop a genetically diverse viral population with an infected individual. Introduction of an antiviral drug into this viral population simply selects for the resistant viral strains by removing the susceptible strains from the pool of infectious particles. This scenario would result in a limited efficacy for any single antiviral agent, and in such an environment, the best strategy is likely to be a combination therapy which makes use of drugs which do not show cross-resistance. Structurally, the 4-hydroxypyrone-based inhibitors are radically different from existing peptide-derived protease inhibitors, and this increases the probability

that the two groups of inhibitors will select for different resistant strains of the virus. Consequently, this new class of protease inhibitors promises to be an important addition to the arsenal of antiviral drugs that will apparently be necessary for a variable treatment of HIV infection.

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Date: 07/19/2000
Time: 10:17

	Type	Hits	Search Text
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3	BRS	2281	(TNF-ALPHA OR (TNF ADJ ALPHA))
4	BRS	29	(((TACE OR ((TNF-ALPHA OR (TNF ADJ ALPHA)) NEAR3 (CONVERTASE OR CONVERTING)))) AND (COORDINATES OR X-RAY OR MODEL OR CRYSTAL))
5	BRS	28	(((TACE OR ((TNF-ALPHA OR (TNF ADJ ALPHA)) NEAR3 (CONVERTASE OR CONVERTING)))) AND (X-RAY OR MODEL OR CRYSTAL))
6	BRS	18	(TACE and ((TNF-ALPHA OR (TNF ADJ ALPHA)) NEAR3 (CONVERTASE OR CONVERTING)))
7	BRS	4	(((TACE AND ((TNF-ALPHA OR (TNF ADJ ALPHA)) NEAR3 (CONVERTASE OR CONVERTING)))) AND (X-RAY OR CRYSTAL))
8	BRS	1	"9940182".PN.
9	BRS	2	"9925740".PN.
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11	BRS	1	au-9925740-$.did.

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4	USPAT; EPO; JPO; Derwent	2000/07/18 15:58		
5	USPAT; EPO; JPO; Derwent	2000/07/18 15:59		
6	USPAT; EPO; JPO; Derwent	2000/07/18 17:47		
7	USPAT; EPO; JPO; Derwent	2000/07/18 17:47		
8	USPAT; EPO; JPO; Derwent	2000/07/18 18:01		
9	USPAT; EPO; JPO; Derwent	2000/07/18 18:02		
10	USPAT; EPO; JPO; Derwent	2000/07/18 18:03		
11	USPAT; EPO; JPO; Derwent	2000/07/18 18:03		

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